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Research Article

Interferon-α and antisense K-*ras* RNA combination gene therapy against pancreatic cancer

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ABSTRACT

Interferon alpha (IFN-α) is used worldwide for the treatment of a variety of cancers. For pancreatic cancer, recent clinical trials using IFN-α in combination with standard chemotherapeutic drugs showed some antitumor activity of the cytokine, but the effect was not significant enough to enlist pancreatic cancer as a clinically effective target of IFN-α. In general, an improved therapeutic effect and safety are expected for cytokine therapy when given in a gene therapy context, because the technology would allow increased local concentrations of this cytokine in the target sites. In this study, we first examined the antiproliferative effect of IFN-α gene transduction into pancreatic cancer cells. The expression of IFN-α effectively induced growth suppression and cell death in pancreatic cancer cells, an effect which appeared to be more prominent when compared with other types of cancers and normal cells. Another strategy we have been developing for pancreatic cancer targets its characteristic genetic aberration, K-*ras* point mutation, and we reported that the expression of antisense K-*ras* RNA significantly suppressed the growth of pancreatic cancer cells. When these two gene therapy strategies are combined, the expression of antisense K-*ras* RNA significantly enhanced IFN-α-induced cell death (1.3- to 3.5-fold), and suppressed subcutaneous growth of pancreatic cancer cells in mice. Because the 2′,5′-oligoadenylate synthetase/RNase L pathway, which is regulated by IFN and induces apoptosis of cells, is activated by double-strand RNA, it is plausible that the double-strand RNA formed by antisense and endogenous K-*ras* RNA enhanced the antitumor activity of IFN-α. This study suggested that the combination of IFN-α and antisense K-*ras* RNA is a promising gene therapy strategy against pancreatic cancer. Copyright © 2004 John Wiley & Sons, Ltd.

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